REMARKS/ARGUMENTS

In the Office Action mailed July 29, 2003, the Restriction Requirement was made final. Claims 45-81 were withdrawn from consideration. The priority claim listed in the specification was required to be amended. A listing of references in the specification was said to not be a proper information disclosure statement. The drawings were said to be informal. An abstract of the disclosure was required. Claim 17 was objected to. Claims 1-44 were rejected under 35 U.S.C. 112, second paragraph. Claims 1-44 were rejected under 35 U.S.C. 112, first paragraph. Claims 1-2, 8-10, 13-15, 17 and 20 were rejected under 35 U.S.C. 102(b). Claims 3-7, 11-12, 16, 18-19 and 21-44 were rejected under 35 U.S.C. 103(a). Applicant respectfully traverses all objections and rejections. Reconsideration and withdrawal of all objections and rejections is respectfully requested.

Restriction Requirement

Applicant does not concede to the characterization of the special technical feature stated in the Office Action or the characterization of the Papp abstract cited. The Papp reference is only directed to nutritional supplementation – there is no disclosure or suggestion of any biomarkers for oxidative stress or methods to detect biomarkers of oxidative stress. Papp suggests supplementation of feeding with sulfur-containing amino acids to improve the antioxidant capacity of premature infants, and giving selenium and vitamin E to high-risk mothers as possibly useful in preventing retinopathy in premature infants.

Priority Claim

The priority claim present as the first sentence of the specification following the title has been amended to conform to current rules and list the PCT priority application, as helpfully suggested by the Examiner.

Information Disclosure Statement

The Office Action indicated that listing references in the specification does not constitute an information disclosure statement. Information disclosure statements were filed by Applicant on January 3, 2003 and July 2, 2002 and the references contained therein have been considered by the Examiner, as evidenced by the initialed Form 1449s returned by the Examiner in the Office Action mailed July 29, 2003.

Drawings

The Office Action indicated the drawings filed were informal and were acceptable for examination purposes. The Office Action indicated that formal drawings were not required until the application is allowed.

Abstract

The Office Action required an abstract of the disclosure. In response, an abstract of the disclosure has been added.

Objection of claim 17

In the Office Action mailed July 29, 2003, claim 17 was objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Office Action stated "claim 1 is directed to method of detecting a biomarker of oxidative stress which claim 17 is a substantial duplicate reciting detection by any method."

In response, claim 17 has been cancelled as duplicative. The dependency of claim 18 has been amended for consistency. Reconsideration and withdrawal of the objection is respectfully requested.

Rejection of claims 1-44 under 35 U.S.C. 112, second paragraph

A. In the Office Action mailed July 29, 2003, claims 1-44 were rejected under 35 U.S.C. 112, second paragraph as being allegedly indefinite. The Office Action stated: "in claims 1-44

the use of 'antigen binding fragment thereof' is indefinite. It is apparent that the antibody produced from hybridoma cell line KF2.F1 is required to practice the claimed invention. However, the possession of the antibody does not provide sufficient meaning with respect to the infinite antigens with which the antibody may bind. It is suggested that 'antigen binding fragment thereof' be eliminated from the claims in order to obviate this rejection."

In response, applicant does not concede to the rejection or the characterization of the invention in the Office Action, but to advance prosecution the term "antigen binding fragment thereof" has been eliminated from the claims. It is believed this amendment obviates this portion of the rejection. It is noted the hybridoma cell line should be K2.F1.

B. In the Office Action mailed July 29, 2003, claims 1, 23, 37 and 41 were said to be "indefinite in their recitation as methods because the methods do not clearly set forth method steps and there is an absence of a resolution step, which reads back on the preamble of the claimed methods."

In response, it is believed claims 1, 23, 37 and 41 are definite. In claims 1 and 23, the method steps are: (a) contacting a sample containing said biomarker . . . with said antibody. . . and (b) detecting the presence of said biomarker. . . The preamble "an immunoassay method to detect a biomarker of oxidative stress in a biological sample" relates to the resolution step (b). Claim 37 recites a method for detecting the presence of oxidative stress in an organism, said method comprising detecting the presence of an antibody or antigen binding fragment thereof that binds an analyte comprising an oxidized sulfur- or selenium containing amino acid, whereby the presence of said antibody or antigen binding fragment thereof is indicative of the presence of oxidative stress in said organism. The detecting step is a clear method step, and relates back to the preamble. Claim 41 has been amended to clarify a resolution step relating back to the preamble. It is believed these arguments and amendments overcome this portion of the rejection.

C. In the Office Action mailed July 29, 2003, claims 9, 10, 14, 15, 30, 31, 34 and 35 were rejected for the use of "specific and non specific".

In response, the terms "protein specific" and "protein nonspecific" are defined in the specification on page 23, lines 14-18. Claims 9, 14, 30 and 34 have been amended to include the definition of protein nonspecific present in the specification. Claims 10, 15, 31 and 35 have been cancelled without prejudice. It is believed these arguments and amendments overcome this portion of the rejection.

Rejection under 35 U.S.C. 112, first paragraph

In the Office Action mailed July 29, 2003, claims 1-44 were rejected under 35 U.S.C. 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Office Action stated "The written description in this case only sets forth monoclonal antibodies produced from the hybridoma cell line KF2.F1 (see pages 17 and 48) and therefore the written description is not commensurate in scope with the claims drawn to the utility of any antibody or binding fragment thereof." The Office Action continued: "With the exception of hybridoma KF2.F1 (PTA-897) the skilled artisan cannot envision the detailed structure of the encompassed all possible antibodies/binding fragments thereof and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation."

It is noted that there are many processes by which proteins can be oxidatively modified by a number of different agents. Likewise, there is more than one different antibody-based process useful in detecting or studying oxidatively modified proteins.

In response to the rejection, it is noted that the inventors do have evidence of other hybridoma cell lines producing antibody. The inventors have performed three separate experiments involving three different immunizations and fusions that generated antibody-

producing hybridoma cell lines. Each of the experiments involved different mice and constituted three separate and independent experiments. One experiment is described in the Specification (pages 39-46 and Table 3-5). The attached Declaration of inventors Joseph J. Kinkade, Jr. and Ngoc-Anh Le describes two additional experiments and additional data obtained using the methods and description of the application. In the Declaration, six additional clones are specifically described that showed activity toward performic acid oxidized BSA (PAoxBSA).

These additional data show that the inventors, at the time the application was filed, had possession of the claimed invention. Monoclonal antibodies have been produced from three hybridoma cell lines. These antibodies have increased activity to two oxidized proteins.

The Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645, and Training Materials provided by the United States Patent Office also indicate the written description guidelines are satisfied. Pages 59-60 of the Training Materials are directed to antibodies. The example provided in the Training Materials is directly analogous. In the example, contemplation but not teaching of antibodies which bind to antigen X is sufficient to satisfy the Written Description Requirement. In this case, multiple antibodies which bind to biomarkers of oxidative stress have been prepared, thus satisfying the Written Description Guidelines and showing possession of the claimed invention at the time of filing.

New claims 82-84 have been added which specify the antibody is produced by K2.F1. These new claims read on the elected group. At the very least, these claims should be allowable.

Claims 1-44 were rejected under 35 U.S.C. 112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabled for the method employing an antibody or antigen

binding fragment thereof for binding a biomarker of oxidative stress because the instant specification is not in compliance with the biological deposit rules."

In response, it is noted a biological deposit was made on October 29, 1999 under the provisos of the Budapest Treaty. The specification on page 48, lines 21-22 describes the deposit date, deposit number and name of the depository. The deposit was made before the filing of the International Application of which the subject application is the national stage. The specification on page 48, line 22 has been amended to add the address of the depository. At the time the deposit was made, the American Type Culture Collection revised its numbering system for patent deposits and did not permit the ATCC acronym to be used when citing the deposit number in the patent application. (See attached notification from Barbara M. Hailey, Administrator of the ATCC Patent Depository). Therefore, it is believed the identifying information is correct.

The Office Action required filing of an affidavit or declaration by applicants, assignees or attorney of record stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository.

It is not seen in the Rules where such a Declaration or affidavit is required. In making the deposit with the ATCC, the statements that the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository were required in order for the deposit to be accepted. It is believed this information overcomes this rejection. Reconsideration and withdrawal of the rejection is respectfully requested. If this rejection is repeated, however, the required affidavit or declaration will be submitted.

Rejection of claims 1-2, 8-10, 13-15, 17 and 20 under 35 U.S.C. 102(b)

In the Office Action mailed July 29, 2003, claims 1-2, 8-10, 13-15, 17 and 20 were rejected under 35 U.S.C. 102(b) over Osawa (Shipin Kexue Taipei, 24(6), Abstract Only, 1997).

The Osawa reference is not believed a proper reference under 35 U.S.C. 102(b). The subject application is the national stage of PCT/US99/26133, filed November 5, 1999. PCT/US99/26133 takes priority from US provisional application 60/107,404, filed November 6, 1998. The Osawa reference is dated 1997, but no month is provided for the publication. According to the Board of Patent Appeals and Interferences, the initial burden of establishing that a document is a prior art publication rests with the Examiner (Ex parte Natale, 11 USPQ2d 1222, 1226 (Bd. Pat. App. & Int'f 1989). Without further information, it is assumed the reference is dated less than one year before the priority date of the subject application. Therefore, the Osawa reference is not a proper 102(b) reference, and the rejection should be withdrawn.

Even if it is shown that Osawa is a proper reference, the claims are not anticipated by the Osawa reference. The Office Action stated "Osawa teaches methods of assessing lipid hydroxyperoxides and secondary products of oxidative breakdown in numerous plant materials. The reaction products are important biomarkers for antioxidative activity of dietary antioxidants. Specifically the reference employs monoclonal and polyclonal antibodies in immunochemical detection methods to measure the antioxidants."

The statements in the Office Action are not entirely accurate. The actual text of the Osawa reference cited is repeated here. The Osawa reference cited states "the oxidative breakdown of membrane polyunsatd. fatty acids is known to be accompanied by the formation of a complex mixt. of lipid hydroperoxides and secondary products. These compds. are highly reactive and are capable of rapid reaction with cellular nucleophiles, such as phospholipids and proteins. We found that these reaction products are candidates as important biomarkers for evaluating the antioxidative activity of dietary antioxidants. We have been involved in

developing immunochem. detection methods for oxidative stress through application of polyclonal and monoclonal antibodies." (emphasis added).

Contrary to the characterization of the Osawa reference in the Office Action, the Osawa reference states the complex mixture of lipid hydroperoxides and secondary products formed from oxidative breakdown of membrane polyunsaturated fatty acids are candidates as biomarkers for evaluating the antioxidative activity of dietary antioxidants, not important biomarkers for antioxidative activity of dietary antioxidants, as stated in the Office Action. There is no teaching in the Osawa reference in selecting which compounds from the complex mixture of breakdown products would be biomarkers for evaluating the antioxidative activity of dietary antioxidants.

Importantly, the Osawa reference states "Based on our hypothesis that endogenous antioxidants in plants must play and important role in antioxidative defense systems by causing stress, and intensive search for novel types of natural antioxidants has been carried out on numerous plant materials, including those used as foods, and we have isolated and identified a no. of lipid-sol. and water-sol. dietary antioxidants from crop seeds, sesame seeds and some spices. In this paper, we review recent progress in research on the functions of dietary antioxidants." If the endogenous antioxidants in plants studied by Osawa cause stress, they would not be useful as biomarkers of oxidative stress, since it would be impossible to determine if the oxidative stress was caused by the endogenous antioxidants in plants or the oxidative breakdown of membrane polyunsaturated fatty acids described by the Osawa reference.

In addition, the claims are not anticipated by the Osawa reference. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" (Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

Independent claim 1 is repeated here.

1. An immunoassay method to detect a biomarker of oxidative stress in a biological sample utilizing an antibody which binds said biomarker of oxidative stress, said method comprising the steps of:

(a) contacting a sample containing said biomarker of oxidative stress with said antibody under conditions which allow binding of said biomarker of oxidative stress to said antibody;

(b) detecting the presence of said biomarker of oxidative stress in said sample.

The Osawa reference does not contain any teaching of a biomarker of oxidative stress. Giving the Osawa reference the broadest interpretation possible, the Osawa reference mentions a complex mixture of lipid hydroperoxides and secondary products formed by oxidative breakdown of membrane polyunsaturated fatty acids. The lipid hydroperoxides and secondary products are disclosed as candidates as biomarkers for evaluating the antioxidative activity of dietary antioxidants. No compounds are disclosed in the Osawa reference and no constituent candidates in the complex mixture are taught as biomarkers of oxidative stress. In addition, there is no teaching of contacting a sample containing a biomarker of oxidative stress with an antibody or antigen binding fragment thereof under conditions which allow binding of said biomarker of oxidative stress to said antibody or antigen binding fragment thereof. The only discussion of antibodies in the Osawa reference follows: "We have been involved in developing immunochemical detection methods for oxidative stress through application of polyclonal and monoclonal antibodies." This statement does not contain teachings of an immunoassay method to detect a biomarker of oxidative stress in a biological sample utilizing an antibody or antigen binding fragment thereof which binds said biomarker of oxidative stress as claimed in the subject application. If there is no teaching of a biomarker of oxidative stress, there can be no teaching of an antibody or antigen binding fragment thereof which binds the biomarker of oxidative stress.

In view of the above, the Osawa reference is either not a proper reference under 102(b) or the claims are not anticipated by the Osawa reference. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of claims 3-7, 11-12, 16, 18-19 and 21-44 under 35 U.S.C. 103(a)

In the Office Action mailed July 29, 2003, claims 3-7, 11-12, 16, 18-19 and 21-44 were rejected under 35 U.S.C. 103(a) over Osawa in view of Ding et al (Journal of Biochemistry, 1998, 332, pages 251-255) in further view of Roberts et al. (US patent 5,700,654).

Claims 3-4, 12, 18-19 and 21-22 do not recite biomarkers of oxidative stress which is an oxidized sulfur- or selenium-containing amino acid, which is stated as the basis of the 103(a) rejection. Therefore, it is believed this rejection should only apply to claims 5-7, 11, 16 and 23-44.

The Office Action stated "Osawa differs from the instant invention in not specifically teaching an antibody specific for oxidized sulfur or selenium containing amino acid compositions. In response, the Osawa reference is discussed above. The Osawa reference is not believed to be a proper reference under 102(b) or in the alternative, the claims are clearly not anticipated by the Osawa reference.

The Office Action stated "Ding et al. teach an antibody which detects selenium. The selenium containing catalytic antibody Se-4A4. The antibody binding characteristics are useful in monitoring free radical activity (damage and protection). See abstract and pages 251 Introduction. The antibodies were produced in mice and tested in an ELISA protocol. Pages 251-252." In the Ding reference, the selenium containing antibody Se-4A4 is described as able to protect mitochondria from free-radical damage. No description is given in the Ding reference of monitoring free radical activity.

The Office Action stated: "although Ding et al. are silent with respect to the catalytic activity being oxidation, Roberts et al. teach the importance of oxidation state in the assessment of oxidation stress." Contrary to the characterization in the Office Action, the Roberts reference does not teach anything about sulfur-containing proteins as markers of oxidative stress. The only mention of sulfur-containing proteins is in the background section of the Roberts reference,

where the problem addressed by the invention: method to assess oxidative stress in vivo by quantification of prostaglandin-like compounds and their metabolites produced by noncyclooxygenase free radical catalyzed mechanism (column 1, lines 10-14) is discussed. Free radicals are short lived, and indirect methods of detection are required. A number of standard detection methods are listed in the background section, including "detection of oxidized products from proteins (e.g., methionine sulfoxide from methionine)" (column 1, lines 26-27, 51-52). The detection method in the Roberts reference is the production of prostaglandin F2-like compounds in plasma increases in response to agents that cause free radical induced lipid peroxidation. The prostaglandin F2-like compounds studied in the Roberts reference do not contain sulfur. Therefore, the Roberts reference is not relevant.

The Office Action stated "it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an antibody that binds oxidized sulfur or selenium containing amino acids as taught by Ding et al. in view of Roberts et al. in the oxidative breakdown process of Osawa because Ding et al. teach that the antibodies against selenium was useful in evaluating oxidative damage and protection (page 251) while, Roberts disclosed that the oxidative state is further crucial in the oxidative measurements (column 1). One of ordinary skill in the art would have been motivated to include an antibody to measure selenium in order to take advantage of antibody specific binding and further measure the oxidation state in order to more precisely understand oxidation as it relates to oxidative stress."

Contrary to the statement in the Office Action, Roberts does not disclose the oxidative state is further crucial in the oxidative measurements. This point is discussed above. It would not have been obvious to substitute the selenium-containing antibody taught by Ding in the oxidative breakdown process of Osawa. Contrary to the statement in the Office Action, Ding does not teach that the antibodies against selenium are useful in evaluating oxidative damage and protection. Ding teaches one selenium-containing antibody as a catalyst in the free-radical damage reaction of mitochondria. There is no teaching or expectation that the selenium-containing antibody disclosed in Ding, or other selenium-containing antibodies would be useful

as catalysts in the oxidative breakdown of membrane polyunsaturated fatty acids of Osawa. In fact, Ding teaches away from the belief that the selenium-containing antibody disclosed in Ding, let alone other selenium-containing antibodies, would be useful as catalysts in reactions in Osawa. Ding discusses examination of thiols as substrates for the peroxidase reaction catalyzed by the Se-4A4 antibody on page 254. Only one thiol compound was able to serve as a substrate for Se-4A4. Ding states "these results should not be surprising, since enzymes have evolved to bind specific substrates, and this specificity is one of their most desirable properties" (page 254). Therefore, it would be very unexpected and surprising if the use of the selenium-containing antibody disclosed in Ding would be useful in the reactions disclosed in Osawa.

In order for a prima facie case of obviousness to be made, first, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In this case, there is no prima facie case of obviousness made. First, there is no suggestion or motivation to modify the references or combine reference teachings. Osawa is directed to identifying lipid-soluble and water-soluble dietary antioxidants from crop seeds, sesame seeds and some spices to study the effect that these compounds have on causing oxidative stress in plants. Ding is directed to the selenium-containing antibody Se-4A4 for use as a catalyst in the reaction of hydroperoxide with mitochondria. Roberts is directed to a method for assessing oxidative stress in vivo using prostaglandin F2-like compounds. The reactions described in the references and the compounds used are completely different. The modification of reference teachings is taught away from, as discussed above.

Second, there is no reasonable expectation of success in modifying reference teachings or combining the references. This point is discussed further above.

Third, not all claim limitations are taught or suggested by the references. In the claims of the invention, the biomarker of oxidative stress is contacted with an antibody or antigen binding fragment thereof. This combination is not found in any combination of references. None of the references teaches or suggests a biomarker for oxidative stress and an antibody or antigen fragment thereof.

In view of the above arguments and amendments, it is believed the rejection is overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above arguments and amendments, it is believed claims 1-9, 11-14, 16, 18-30, 32-34, 36-44 and 81-84 are allowable. Reconsideration and withdrawal of the rejections is respectfully requested. If there are any issues remaining to patentability, the Examiner is respectfully requested to telephone the undersigned.

It is believed that a three-month extension of time is required for this submission. Accordingly, a petition for a three-month extension of time and a check in the amount of $475.00 are included with this response. In addition, three dependent claims are added. However, four claims have been cancelled, so it is believed no additional claims fees are due.

It is believed that the present submission does not require the payment of any additional fees. If this is incorrect however, please charge any fees required, including any extensions of time required, to Deposit Account No. 07-1969.

Respectfully submitted,

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